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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/225,718	01/06/99	TRECU	07230/013004

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EXAMINER	
KETTER, J	
ART UNIT	PAPER NUMBER
1636	20

DATE MAILED: 10/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/225,718	Applicant(s) TRECO ET AL.	
	Examiner James Ketter	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/23/01 .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 66-168 is/are pending in the application.

4a) Of the above claim(s) 66-113 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 114-168 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Tita Adams

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 18 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 66-113 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 114-168 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in Paper No. 16, mailed 29 January 2001.

At pages 3 and 4 of the amendment filed 23 July 2001, Applicants argue that the claimed method is limited to ex vivo embodiments. This is correct. The point raised in the previous Office Action regarding targeting moieties is thus moot. Applicants also argue at page 3 that no aspect of the rejection applies to ex vivo methods. Clearly, both in vivo and ex vivo methods were addressed in the previous Office Action, and are discussed at least in Verma et al. and French Anderson.

At the second paragraph at page 4, Applicants state that it appears to them that the Office Action requires certain specific information. However, no such requirement is or was made. The lack of such information is, however, a significant factor to be considered in determining whether the claimed invention is enabled.

At the third paragraph at page 4, Applicants state that the particular construct used "is not what dictates dosage." However, in view of the teachings of French Anderson,

the editorial from Nature Biotechnology, and Verma et al., it is clear that the stability and longevity of expression of the gene is dependent, in part, on the vector system. Applicants then argue that adjusting the dosage by adjusting the number of transfected cells administered is "a simple and routine task". However, in view of the novelty of Applicants' invention, how could such a method have been routine in the prior art? In view of the complete lack of clinical success in the art of gene therapy, including ex vivo methods, it is not apparent that transplanting genetically modified cells would have been regarded by the skilled practitioner as routine.

At the first paragraph at page 5, and the subsequent paragraph, Applicants argue that protein therapy was well known at the time of filing, citing several references demonstrating this. However, it is clear that administering a protein composition to a patient is not analogous to administering a nucleic acid composition that encodes said protein. Neither the specification nor the art teaches how such a conversion calculation would be made. Applicants had argued in the last paragraph at page 4 that if too little protein is expressed, more cells could be implanted into the patient. However, this is trial-and-error experimentation performed directly on the patient, which would have been deemed undue experimentation.

At the first full paragraph at page 6, Applicants argue that setting forth treatment regimens for every conceivable disorder would not have been feasible. While it is correct that no requirement exists for such disclosure where the prior art and/or empirical experimentation would have been sufficient, it is maintained that the prior art and empirical experimentation were not sufficient. It is noted that not even one detailed example or prophetic example is offered in the specification. Given that not one

successful protocol was known in the prior art, and that a large amount of experimentation by many workers in the prior art failed to achieve success, it is not clear how one of skill in the art would have been expected to proceed in practicing the claimed invention. Further in the paragraph, Applicants draw an analogy to a claimed syringe. However, the distinction between such a claimed syringe and the instant invention is clear—the syringe art is well developed and full of successes in delivering a variety of compositions to patients. The gene therapy art is devoid of such prior art successes.

At the paragraph bridging pages 6 and 7, and at the full paragraphs at page 7, Applicants argue that Orkin et al. and French Anderson do not apply to the instant invention. Particularly, it is argued that persistence of expression, which both references as well as Verma et al. (at page 240, paragraph bridging the left-hand and center columns, and bridging the center and left-hand columns) cite as problematic in gene therapy, is not relevant as the cells are selected for expression. However, it is noted first that Orkin et al. does address both in vivo and ex vivo therapies, e.g., at the sixth page, fifth full paragraph, and at the paragraph bridging the seventh and eighth pages. French Anderson, e.g., at page 26, right-hand column, third full paragraph, and Verma et al., e.g., as noted supra, all teach that transfected cells quickly stop expression of transfected genes, whether an in vivo or ex vivo method was employed. Mountain (Y, newly cited), which is cited here in rebuttal to Applicants' contention that expression of genes transfected ex vivo remains stable in vivo, teaches, e.g., at Table 4 at page 122, that non-viral methods of transfection in gene therapy, including ex vivo, do not lead to stable expression of the gene once implanted. Thus, the problem is not in finding highly expressing cells to

implant, but in keeping that expression after implantation. Applicants have not shown that this technological barrier has been broken by the instant invention.

At the paragraph bridging pages 7 and 8, Applicants argue that the teachings of the references, particularly Orkin et al., with respect to the problems of animal models of human genetic disease, are irrelevant, because normal animals were used in the invention, and because the claimed invention "is merely a new method of delivering a protein." However, the claims are clearly drawn to gene therapy methods, as a therapeutic product is being expressed from the DNA. It is not correct to distinguish the claimed invention from gene therapy as being merely a gene transfer method, particularly in view of the specification, which is clearly drawn to the purpose of gene therapy. Furthermore, the recitation of the discussion in Orkin et al. in the previous Office Action was to show that gene therapy is and was recognized as an unpredictable field, where even model systems are not viewed as necessarily trustworthy. Still further, it is not particularly clear to what in vivo tests Applicants are referring.

With respect to Applicants' arguments at the full paragraph at page 8, it is believed that said arguments have been addressed supra.

At the first three paragraphs at page 9, Applicants argue that there would not have been an excessive amount of experimentation to devise an ex vivo gene therapy method, as they contend that ex vivo gene therapy is not unpredictable. Again, as set forth supra, no successes in the field of gene therapy were known in the prior art. The cited references teach that ex vivo gene therapy indeed did exhibit unpredictability of gene expression, and particularly unstable expression.

At the first paragraph at page 10, Applicants argue that the claims are not as broad as interpreted in the previous Office Action, contending that only constructs that function are encompassed. This, however, is a circular argument. Of course, it was not stated or implied that the claims read upon, for example, the use of a completely random DNA segment to treat a particular disease. What was set forth is that the broadest claims are not constrained with respect to the disease or DNA to treat said disease. Applicants go on to argue that there is no evidence that the constructs would not work. However, such arguments already have been addressed supra. Applicants argue that they have shown that transfected, implanted cells show continued expression of the transfected gene. However, as noted supra, it is not clear what showing Applicants are relying upon.

At the first full paragraph at page 11, Applicants argue that the level of skill in the transfection art is high, and that this is a factor weighing toward enablement. However, it is noted that the factor in question is drawn to "relative" skill levels. Given the complete failure of the prior art to produce even one clear demonstration of gene therapy, it is apparent that the skill level in the art is relatively low. Compare to the syringe art, to revisit Applicants' earlier argument. Innovations have been made frequently in the syringe art, as shown, e.g., by the number of patented inventions in that art, and successful syringes have been used for many years. There, the relative skill level is high, as technical problems are more easily surmounted.

Applicant's arguments filed 23 July 2001 have been fully considered but they are not persuasive.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to the directly to the Examiner by facsimile transmission at (703) 746-5155. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993)(see 37 CFR § 1.6(d)). To send the facsimile to the Art Unit instead, the Art Unit 1636 Fax number is (703) 305-7939. NOTE: If Applicant does submit a paper by fax to this number, the Examiner must be notified promptly, to ensure matching of the faxed paper to the application file, and the original signed copy should be retained by Applicant or Applicant's representative. (703) 308-4242 or (703) 305-3014 may be used without notification of the Examiner, with such faxed papers being handled in the manner of mailed responses. Applicant is encouraged to use the latter two fax numbers unless immediate action by the Examiner is required,

e.g., during discussions of claim language for allowable subject matter. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the Examiner with respect to the examination on the merits should be directed to James Ketter whose telephone number is (703) 308-1169. The Examiner normally can be reached on M-F (9:00-6:30), with alternate Fridays off.

Questions regarding formalities and processing of the case should be directed to Zeta Adams, whose telephone number is (703) 305-3291.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's acting supervisor, John LeGuyader, can be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

JAMES KETTER
PRIMARY EXAMINER

Jsk
October 5, 2001